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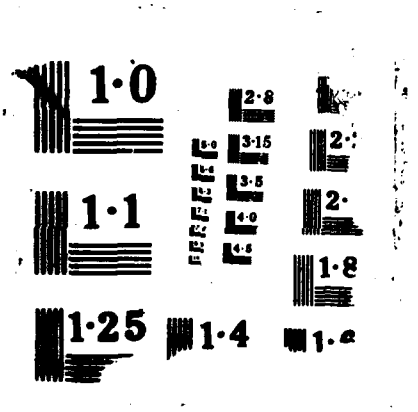
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19. ABSTRACT (*Continue on reverse if necessary and identify by block number*)

This report describes initial studies designed to investigate the effects of a high degree of neurological alertness on brain metabolism. Positron emission tomography (PET) was used to quantitate brain metabolism using fluorodeoxyglucose (FDG) as an indicator of glucose uptake during mental stimulation provided by playing a video game (Mooncrash) for 30 minutes. Brain metabolism in 22 regions during neurological alertness was compared with the resting state. In most subjects there was a marked increase in brain metabolism with stimulation, however there was tremendous variability in brain metabolism in the eight subjects. Consistent patterns of activation were found with maximal activation in primary visual cortex, followed by parieto-occipital cortex, cerebellum and thalamus.

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This research project was activated in early december 1986, due to administrative delays. As stated in the original proposal, the program involved two aspects. First, studies of brain metabolism under situations which approximate a situation of stress. Second, development of tracer molecules for in vivo analyses of beta-adrenergic receptors. Interesting data could be collected on these two aspects of the program and point to several areas important for future investigations.

1. Brain glucose metabolism in a situation of alertness.

The first problem was to define a situation in the laboratory which would generate a high degree of neurological alertness and thus mimick to a certain extent a situation of stress. A good way to achive this would be to use a flight simulator. However, this equipment is not available in our laboratory setting and it was decided, as a first approach,to use a videogame (Mooncrash) as the stressor. The Positron Tomography technique used is the so-called FDG/PET autoradiographic procedure for measurement of glucose metabolism. Briefly, [F-18]-labeled deoxyfluoroglucose, a non metabolized glucose analog, is injected intraveinously into a forearm vein. The tracer input function is sampled from a catheter inserted into a pedial (during stimulation) or radial (studies at rest) artery under local anesthesia. Beginning at injection time or one minute before, the subject is asked to concentrate as much as he can on the game, and is allowed to play for 30 min. After 30 min, more than 90% of the tracer has been incorporated in the brain. The subject is then at rest on the tomograph's bed and FDG uptake is measured with the ECAT III positron camera. Emission density data are converted into estimations of

regional brain glucose metabolism by using the operational equations of Sokoloff , adapted for PET by Phelps.

The subjects for the present studies are young adult males (mean age 22 yrs) recruited from the surrounding community and have a negative neurological history. FDG is given at a moderate dose of 6 mCi, allowing us to perform control studies (without stimulation) on the same subjects. So far, 8 analyses have been performed in the situation of stimulation and repeated at rest. Results of the regional brain glucose utilization (expressed in micromols per 100g brain per min) in the 8 subjects during stimulation at during the study at rest are shown on table I.

Several striking observations can be made on these data. First, there is a tremendous variability in the level of brain glucose metabolism. In most of the subjects, there is a marked increase in metabolism during stimulation on the game. It is worth pointing out that the increase of brain metabolism in an actual situation of stress can only be higher than our estimation, since the stimulation performed in the laboratory setting is hardly maximal. However, it is remarkable and rather unexpected that in 2 subjects, there is no significant differences in the global rate of glucose utilization between the activated and the resting state. Actually, in one patient, metabolic rates were more elevated at rest than during stimulation. The only reasonable interpretation of such a discrepancy is that the mean level of brain glucose utilization at rest can vary in response to several poorly defined factors in addition to its variation with specific stimuli.

This large individual variation certainly hampers the detection of subtle variations of brain metabolic activity in response to environmental

modifications. However, by expressing metabolic rates in percent of a mean gray matter glucose utilization, it is still possible to analyze variations in the pattern of regional glucose utilization in response to stress and other stimuli. These so-called relative metabolic indexes are shown in table II for the 8 subjects sucessfully examined at rest and under submaximal alertness. It is clear from the comparison of the two states that consistent patterns of activation are found. Maximal activation is found in primary visual cortex, followed by parieto-occipital cortex, cerebellum and thalamus. Other regions undergo relatively less activation.

Although they remain quite preliminary, these results point to several interesting questions which should be pursued further. Some of the issues raised may even have isignificant practical implications.

First, a level of metabolic activation such as that observed in some of our subjects has been reported in the litterature only in pathologic conditions (namely in "petit mal" epilepsy). Our data show that brain metabolism, far from being independant of the mental state, can vary in large proportions in response to the environment. We think that this interaction between brain and environment is interesting in itself and should be studied further.

Second, the measurements allow us to make a reasonable estimate of the energetic demands of the brain in situations of maximal stimulation. If we consider a glucose metabolism of at least 10 mg/100g.min for 1 kg of gray matter, we obtain a glucose utilisation of 6 g/h. Again, the actual situation may be of an even higher value. This level of glucose utilization must certainly be attained by pilots, especially when performing specific, non routine missions. It appears reasonable to suggest that, when brain glucose demand reaches this level, even a mild degree of hypoglycemia

which in normal circumstances would be without consequences, may affect subtle brain physiologic parameters such as reaction times. It may thus be interesting to perform estimations of reaction times in different conditions of stress, and at different levels of glycemia. Studies of this type might have significant practical implications. For example, if our preliminary data are confirmed, it might prove useful to achive a physiologic "glucose clamp" in pilots and other personnel experiencing high levels of stimulation and whose responsiveness is critical. Ways to protect against hypoglycemia, usually by increasing liver glycogen reserves, are well known by nutritionists and are apparently being used by some athletes.

2. Development of a tracer for adrenergic receptors.

As stated in the original proposal, our understanding of adrenergic mediation of brain reactions to stress would greatly benefit from reliable methods for in vivo analyses of adrenoceptors. Although PET may provide such a tool in the future, the development of an appropriate tracer certainly requires a lot of work and effort, and must thus be regarded as a medium-term project.

From a radiochemical standpoint, ligands for PET can be labeled with carbon-11 or fluorine-18 (other isotopes being of relatively minor importance). C-11 radiochemistry is more easy to perform than fluorine chemistry, and was selected as the first choice. The first series of experiments aimed at the reliable preparation of methyl iodide, a general purpose reagent for C-11 labeling reactions. An original method for methyl iodide synthesis was recently developed in our laboratory. Compared to other methods, this preparation uses P2I4 in the synthesis of methyliodide, resulting into the production of a strictly anhydrous reagent

In order to assess the quality of the radiolabeled precursor, we chose to produce C-11-N-methylspiperone (NMS), a ligand of dopamine D2 receptors. This molecule was selected since its synthesis has been performed by others previously. It can thus serve as a "gold standard" for our radiochemistry procedures. In addition, our laboratory plans to study dopaminergic receptors in human diseases.

So far, work on adrenoceptor ligands has been focused only on studies of the available literature in order to select candidate ligands for PET. Based upon this literature survey, the beta-receptor ligand pindolol was selected as a possible starting point. Further information, particularly provided by Dr. G.Engel (Sandoz, Basles), suggested that a more recent pindolol derivative, butylpindolol, may be a more promising candidate. Work in various laboratories has clearly shown that propranolol, the best characterized member of the aryloxypropanolamines with affinity for beta-receptors, cannot be used with PET due to its high lipophilicity. Pindolol has given some encouraging results in a few animals studies, although its passage through the blood-brain barrier is not optimal. A recent report suggests that butylpindolol might better than pindolol.

Based on these evidences, our future strategy will be to prepare pindolol or butylpindolol derivatives of increasing lipophilicity, as has been made with spiroperidol derivatives, and check whether these modifications result into some improvement of pharmacokinetic behavior.

Table I

Comparison of glucose metabolic rates in sensorial activation (S A) versus resting state (R S).
(micromol / 100 g . min)

	Subjects	I		II		III		IV		V		VI		VII		VIII	
BRAIN REGIONS		S A	R S	S A	R S	S A	R S	S A	R S	S A	R S	S A	R S	S A	R S	S A	R S
1	Right Frontal Cortex	63.94	42.49	63.92	55.97	61.64	54.89	55.39	34.97	55.21	34.44	52.13	35.34	36.78	41.54	58.63	54.61
2	Left Frontal Cortex	63.06	42.51	64.87	56.00	62.68	57.79	55.24	34.40	56.27	32.61	50.25	35.70	38.68	42.41	56.41	54.03
3	Right Temporal Cortex	60.72	37.67	60.94	46.32	62.07	50.60	47.86	31.04	45.97	28.81	43.77	29.12	33.28	34.35	50.58	45.27
4	Left Temporal Cortex	57.22	36.71	61.75	50.46	59.35	53.00	50.40	31.93	50.85	29.88	45.45	28.51	31.26	35.03	48.61	45.14
5	Right motor Cortex	67.72	42.27	65.51	53.61	65.17	57.97	55.24	34.74	57.78	39.08	50.08	36.46			60.19	56.10
6	Left motor Cortex	61.94	42.54	68.15	57.00	65.14	60.18	56.88	34.95	57.81	38.75	51.60	37.53			55.82	56.31
7	Right Parietal Cx	57.17	36.69	59.91	49.70	57.09	50.74	46.10	28.27	43.27	30.25	43.78	29.81			49.71	47.73
8	Left Parietal Cx	56.39	36.98	58.04	48.46	55.87	51.81	48.96	28.79	45.14	31.03	46.31	28.83			49.93	47.05
9	Right Par-occ Cortex	58.61	35.52	61.02	51.00	61.05	46.21	51.74	28.83	49.80	28.86	47.98	28.57	33.18	37.03	52.33	48.00
10	Left Par-occ Cortex	55.56	36.10	60.38	50.67	60.14	47.79	55.32	27.29	51.93	28.22	46.11	28.07	32.64	36.40	51.12	47.24
11	Right Visual Cortex	72.94	42.81	77.23	49.38	73.85	55.82	69.06	34.46	58.79	32.11	61.71	35.49	50.26	42.29	67.45	54.81
12	Left Visual Cortex	72.66	43.04	78.19	50.03	75.16	55.35	70.37	33.48	57.16	31.09	59.84	35.34	48.81	41.81	63.71	52.29
13	Right Insula	59.67	36.74	60.07	50.72	58.40	51.73	49.05	30.91	47.35	30.16	46.92	30.02	35.42	36.09	54.49	48.18
14	Left Insula	58.50	36.21	61.54	51.87	59.30	51.95	48.74	29.53	49.22	30.40	46.12	27.90	34.47	35.67	52.21	49.56
15	Right Striatum	61.78	39.52	61.30	53.47	62.30	56.47	51.27	31.24	47.36	29.11	45.27	31.67	37.31	38.06	56.00	50.81
16	Left Striatum	62.22	37.34	66.20	54.92	63.51	54.63	50.37	31.78	47.18	28.21	44.34	31.39	37.16	38.82	57.10	52.46
17	Right Thalamus	57.00	33.42	64.92	48.35	60.25	52.29	48.48	30.23	54.55	31.88	46.93	30.69	40.55	35.30	54.17	46.37
18	Left Thalamus	55.44	34.79	68.99	50.95	58.97	51.22	48.29	30.46	53.21	32.37	44.61	31.70	37.82	35.48	55.13	46.08
19	Right Frontomesial Cx	61.22	40.22	64.05	56.49	56.38	54.14	50.58	33.67	53.33	34.84	48.60	34.28	37.62	38.13	56.31	52.81
20	Left Frontomesial Cx	62.06	40.15	64.14	57.53	58.45	54.84	51.27	35.14	54.58	35.87	47.90	33.80	36.93	39.03	57.82	52.07
21	Right Cerebellum	51.94	27.65	52.28	44.60	61.50	47.63	50.40	28.07	41.51	26.57	41.70	26.83	37.61	28.66	46.32	42.48
22	Left Cerebellum	51.61	26.63	53.08	44.57	60.55	49.65	52.63	27.60	44.52	27.16	42.87	26.15	38.71	27.90	46.24	41.80
MEAN GRAY MATTER																	
RIGHT HEMISPHERE		63.16	37.93	63.76	51.70	62.35	50.99	54.49	32.66	52.95	32.15	50.50	31.36	38.46	36.67	56.88	51.86
LEFT HEMISPHERE		59.33	37.44	63.08	51.78	63.31	52.42	55.94	31.38	53.21	31.11	48.80	30.52	38.68	37.77	52.85	50.60

Table 1: Comparison of relative metabolic rates in sensorial activation (S A) versus resting state (R S).
(% of mean global glucose metabolism)

Subjects	I		II		III		IV		V		VI		VII		VIII	
BRAIN REGIONS	S A	R S	S A	R S	S A	R S	S A	R S	S A	R S	S A	R S	S A	R S	S A	R S
1 Right Frontal Cortex	103.97	112.75	100.79	108.18	98.10	106.16	100.32	109.21	104.41	108.88	104.99	114.22	95.36	111.61	106.86	106.60
2 Left Frontal Cortex	102.53	112.80	102.29	108.23	99.76	111.77	100.05	107.43	106.41	103.10	101.21	115.38	100.29	113.94	102.82	105.47
3 Right Temporal Cortex	98.74	99.96	96.09	89.52	98.79	97.87	86.68	96.94	86.93	91.08	88.16	94.12	86.28	92.29	92.19	88.37
4 Left Temporal Cortex	93.04	97.41	97.37	97.53	94.46	102.91	91.28	99.72	9[illegible].16	94.47	91.54	92.15	81.05	94.19	88.60	88.11
5 Right motor Cortex																
6 Left motor Cortex																
7 Right Parietal Cx																
8 Left Parietal Cx																
9 Right Par-occ Cortex	95.30	94.26	96.21	98.57	97.17	89.37	93.71	90.04	94.18	91.24	96.64	92.34	86.03	99.49	95.38	93.70
10 Left Par-occ Cortex	90.33	95.80	95.20	97.93	95.72	92.43	100.19	85.23	98.20	89.21	92.87	90.72	84.63	97.80	93.17	92.21
11 Right Visual Cortex	118.61	113.60	121.78	99.44	117.54	107.96	125.07	107.62	111.18	101.52	124.29	114.71	130.21	113.62	115.80	106.99
12 Left Visual Cortex	118.16	114.21	123.29	96.70	119.62	107.05	127.45	104.56	108.09	98.29	120.52	114.22	126.55	112.33	111.63	102.07
13 Right Insula	97.02	97.49	94.72	98.03	92.95	100.05	88.84	96.53	89.54	95.35	94.50	97.03	91.83	96.96	99.32	94.05
14 Left Insula	95.12	96.09	97.04	100.25	94.38	100.47	88.28	92.22	93.07	96.11	92.89	90.17	89.37	95.84	95.16	96.74
15 Right Striatum	100.45	104.87	96.66	103.34	99.16	109.22	92.86	97.56	89.56	92.03	91.18	102.36	96.73	102.26	102.07	99.18
16 Left Striatum	101.17	99.08	104.38	106.15	101.08	105.66	91.23	99.25	99.22	89.19	89.31	101.45	96.34	104.30	104.07	102.40
17 Right Thalamus	92.68	88.69	102.37	93.45	95.89	101.13	87.80	94.41	103.16	100.79	94.52	99.19	105.19	94.84	98.73	90.51
18 Left Thalamus	90.15	92.33	108.78	98.47	93.86	99.06	87.46	95.13	100.62	102.34	89.84	102.46	90.06	95.39	100.48	89.95
19 Right Frontomesial Cx	99.55	106.73	100.99	109.18	89.73	104.71	91.61	105.15	100.85	110.15	97.88	110.80	97.54	102.44	102.63	103.08
20 Left Frontomesial Cx	100.70	106.54	101.14	111.19	93.02	106.06	92.86	109.74	103.21	113.40	96.47	109.24	95.75	104.86	105.39	101.64
[illegible] Cerebellum	84.46	73.37	82.43	86.20	97.88	92.12	91.28	87.66	78.50	84.00	83.99	86.72	97.53	77.00	84.43	82.92
[illegible] Cerebellum	83.92	70.66	83.70	86.14	96.37	96.03	95.32	86.20	84.19	85.87	86.34	84.52	100.36	74.96	84.28	81.59

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